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Abstract: Background and aims: Inflammation is part of the pathophysiology of congestive heart failure (CHF). However, little is known about the impact of the presence of systemic inflammatory disease (SID), defined as inflammatory syndrome with constitutional symptoms and involvement of at least two organs as co-morbidity on the clinical course and prognosis of patients with CHF. Methods and results: This is an analysis of all 622 patients included in TIME-CHF. After an 18 months follow-up, outcomes of patients with and without SID were compared. Primary endpoint was all-cause hospitalization free survival. Secondary endpoints were overall survival and CHF hospitalization free survival. At baseline, 38 patients had history of SID (6.1%). These patients had higher N-terminal pro brain natriuretic peptide and worse renal function than patients without SID. SID was a risk factor for adverse outcome [primary endpoint: hazard ratio (HR) = 1.73 (95% confidence interval: 1.18-2.55, P = 0.005); survival: HR = 2.60 (1.49-4.55, P = 0.001); CHF hospitalization free survival: HR = 2.3 (1.45-3.65, P < 0.001)]. In multivariate models, SID remained the strongest independent risk factor for survival and CHF hospitalization free survival. Conclusions: In elderly patients with CHF, SID is independently accompanied with adverse outcome. Given the increasing prevalence of SID in the elderly population, these findings are clinically important for both risk stratification and patient management

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Prognostic impact of systemic inflammatory diseases in elderly patients with congestive heart failure

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Summary

Background and aims: Inflammation is part of the pathophysiology of congestive heart failure (CHF). However, little is known about the impact of the presence of systemic inflammatory disease (SID), defined as inflammatory syndrome with constitutional symptoms and involvement of at least two organs as co-morbidity on the clinical course and prognosis of patients with CHF.

Methods and results: This is an analysis of all 622 patients included in TIME-CHF. After an 18 months follow-up, outcomes of patients with and without SID were compared. Primary endpoint was all-cause hospitalization free survival. Secondary endpoints were overall survival and CHF hospitalization free survival. At baseline, 38 patients had history of SID (6.1%). These patients had higher N-terminal

pro brain natriuretic peptide and worse renal function than patients without SID. SID was a risk factor for adverse outcome [primary endpoint: hazard ratio (HR)=1.73 (95% confidence interval: 1.18–2.55, $P=0.005$); survival: HR=2.60 (1.49–4.55, $P=0.001$); CHF hospitalization free survival: HR=2.3 (1.45–3.65, $P<0.001$)]. In multivariate models, SID remained the strongest independent risk factor for survival and CHF hospitalization free survival.

Conclusions: In elderly patients with CHF, SID is independently accompanied with adverse outcome. Given the increasing prevalence of SID in the elderly population, these findings are clinically important for both risk stratification and patient management.

Introduction

Despite substantial progress in the management of congestive heart failure (CHF), morbidity and mortality remain unacceptably high.^{1–3} In addition to progression of CHF, non-cardiac co-morbidities may negatively impact the course of disease. Identification of such CHF modifying co-morbidities

is not only crucial for risk stratification but it may also influence treatment of individual patients.

Since the early 1990s when Levine *et al.*⁴ reported on elevated levels of an inflammatory cytokine—i.e. tumour necrosis factor (TNF)—in patients with CHF, the link between CHF and inflammation is established. Meanwhile, a number of studies have demonstrated that inflammation may contribute to

the pathophysiology and disease progression in CHF and that inflammatory biomarkers correlate with disease severity and outcome.^{5,6}

However, little is known about the impact of non-cardiac co-morbidities that are associated with chronic inflammation on disease progression and prognosis in CHF. Since systemic inflammation is the key factor, systemic inflammatory diseases (SIDs) may be particularly relevant in this regard. SID can be defined as inflammatory syndromes with constitutional or general symptoms and involvement of different organ systems. They include vasculitic and connective tissue diseases such as giant cell arteritis (GCA), polymyalgia rheumatica (PMR), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).^{7,8} Because of their high prevalence in the elderly, RA, PMR and GCA are of special clinical importance in populations with chronic diseases such as CHF.^{9,10}

To determine the impact of SID on the clinical course and prognosis of CHF in elderly patients, we performed a *post hoc* analysis of the prospective randomized controlled multicentre trial of intensified vs. standard medical therapy in elderly patients with CHF (TIME-CHF). This trial was designed to compare 18 months outcomes of N-terminal pro brain natriuretic peptide (NT-proBNP)-guided vs. symptom-guided therapy in patients aged 60 years or older with symptomatic CHF.¹¹

Methods

TIME-CHF study

The detailed study design and methods of the multicentre TIME-CHF study¹¹ and the principal findings of pts with depressed LV function have been reported in detail previously.¹² In brief, patients aged ≥ 60 years with dyspnoea New York Heart Association function class (NYHA) \geq II on current therapy, a history of hospitalization for CHF within the last year and elevated NT-proBNP levels were included. Excluded were patients as previously defined.¹¹ Overall, 622 patients were included and stratified by age and left ventricular ejection fraction (LVEF). Patients were randomized into two treatment strategies, i.e. symptom-guided or intensified NT-proBNP-guided therapy. Medical therapy was prescribed according to current guidelines with predefined escalating rules to reduce either symptoms or NT-proBNP levels to predefined target values. Patients were followed up in the outpatient clinics of each centre with prespecified visits after 1, 3, 6, 12 and 18 months.

At inclusion, patient history was taken. SID was defined as the diagnosis of one of the following

diseases: PMR, GCA, RA/polyarthritis, SLE, Sjogren's syndrome (SS), dermatomyositis, polymyositis (PM), systemic sclerosis, remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) and spondylitis ankylosing (SA). Presence of SID was reported by local investigator and for this analysis verified centrally by a second review of individual hospital charts. Charlson score was used as a marker of global morbidity as previously described. In brief more than 5 indicate a very high co-morbidity class, whereas 3–4, 1–2 or 0 points indicate high, medium or low co-morbidity classes, respectively.¹³

The primary endpoint of TIME-CHF was all-cause hospitalization free survival. Secondary endpoints were survival and heart failure hospitalization free survival. Per protocol, cancer-related death and hospitalizations were not considered as endpoints.

Statistical analysis

Results are presented as frequencies, mean (SD) or median (interquartile range), as appropriate. Between-group comparisons were performed using Student's *t*-test, Mann–Whitney *U*-test or Pearson chi-square-test, as appropriate. Kaplan–Meier curves were used for calculating time-dependent occurrences of events. For comparison between groups, the log-rank test was used. Hazard ratio (HR) was derived from univariable Cox regression and tested for independence using multivariable Cox regression entering gender, age, body mass index, LVEF, coronary artery disease (CAD), cardiovascular risk factors, other co-morbidities, symptoms and clinical signs of CHF, blood pressure (BP), heart rate, creatinine, NT-proBNP, QRS width, medication including non-steroidal antirheumatic drugs (NSAID) and corticosteroids as co-variables.

A two-sided *P*-value of 0.05 was considered to be statistically significant. All calculations were performed with the use of the SPSS statistical package version 15.0 (SPSS Inc, Chicago, IL, USA).

Results

Thirty-eight of the 622 patients (6.1%) were classified as having SID at baseline. Baseline characteristics of patients with and without SID are shown in Table 1. Patients with SID suffered significantly more from inflammatory bowel disease and osteoporosis, had higher NT-proBNP and serum creatinine values. Their baseline medication included more often NSAIDs and corticosteroids. There was no difference, however, in heart failure medication between the two groups. As shown in Table 2, most patients had PMR, GCA or RA as the SID-defining diagnosis.

Table 1 Baseline characteristics

| | No SID <i>n</i> = 584 | SID <i>n</i> = 38 | <i>P</i> -value |
|------------------------------------|--------------------------|----------------------|-----------------|
| Age (years) | 76.9 ± 7.6 | 76.5 ± 6.7 | 0.69 |
| Female (%) | 232 (39.7) | 21 (55.3) | 0.059 |
| NT-proBNP-guided therapy (%) | 289 (49.5) | 21 (55.3) | 0.49 |
| Systolic dysfunction (%) | 469 (80.3) | 30 (78.9) | 0.838 |
| Body mass index | 25.7 ± 4.4 | 25.1 ± 4.7 | 0.477 |
| LVEF% | 35 ± 13 | 34 ± 14 | 0.464 |
| NT-proBNP (pg/ml) | 3736 (1903–6837) | 4940 (2689–8143) | 0.048 |
| Creatinine (mg/dl) | 115 ± 38 | 128 ± 40 | 0.05 |
| CRP (mg/l) | 9.0 (0–14) | 9.5 (1–32) | 0.206 |
| Heart rate (beats/min) | 75 ± 14 | 78 ± 14 | 0.30 |
| Systolic BP (mmHg) | 122 ± 20 | 123 ± 22 | 0.744 |
| Primary cause of heart failure (%) | | | |
| CAD | 312 (53.4) | 18 (47.4) | 0.808 |
| Dilated cardiomyopathy | 84 (14.4) | 5 (13.2) | |
| Valvular heart disease | 21 (3.6) | 2 (5.3) | |
| Hypertensive heart disease | 160 (27.4) | 13 (34.2) | |
| Other | 7 (1.2) | 0 | |
| Co-morbidities (%) | | | |
| Previous myocardial infarction | 272 (46.6) | 14 (36.8) | 0.243 |
| Hypertension | 433 (74.1) | 29 (76.3) | 0.767 |
| Diabetes mellitus | 209 (35.8) | 13 (34.2) | 0.844 |
| Insulin dependent DM | 81 (13.9) | 2 (5.3) | 0.131 |
| Stroke/transient ischaemic attack | 92 (15.8) | 6 (15.8) | 0.995 |
| COPD | 118 (20.2) | 6 (15.8) | 0.509 |
| Kidney disease | 331 (56.7) | 24 (63.2) | 0.434 |
| Cancer | 84 (14.4) | 2 (5.3) | 0.115 |
| Inflammatory bowel disease | 8 (1.8) | 3 (7.9) | 0.003 |
| Osteoporosis | 60 (10.3) | 10 (26.3) | 0.002 |
| Charlson score | 3 (2–4) | 3 (2–5) | 0.35 |
| Medication (%) | | | |
| NSAID | 110 (18.8) | 13 (34.2) | 0.021 |
| NSAID on demand | 33 (5.7) | 3 (7.9) | 0.566 |
| Corticosteroids | 81 (13.9) | 20 (52.6) | <0.001 |
| ACE-inhibitor or ARB | 541 (92.6) | 38 (100) | 0.083 |
| β-Blocker | 449 (76.9) | 27 (71.1) | 0.411 |
| Spironolactone | 217 (37.2) | 17 (44.7) | 0.354 |
| Loop diuretics | 540 (92.5) | 35 (92.1) | 0.935 |

Data are given as counts and percentages, mean ± SD or median (interquartile range) as appropriate. DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; ARB, angiotensin receptor blocker.

Table 2 Different SIDs at baseline

| SID | <i>n</i> = 38 |
|------------------|---------------|
| PMR/GCA | 18 |
| RA/polyarthritis | 7 |
| SA | 2 |
| SS | 1 |
| SLE | 1 |
| RS3PE | 1 |
| PM | 1 |
| Not specified | 7 |

During the 18-month follow-up, patients with SID exhibited a significantly worse outcome than patients without SID. Thus, all-cause hospitalization free survival was 26.3% vs. 40.6% [$P=0.006$, Figure 1a; HR=1.73 (95% confidence interval (CI) 1.18–2.55), $P=0.005$], overall 18-month survival 63.2% vs. 81.5% [$P=0.001$, Figure 1b; HR=2.60 (95% CI 1.49–4.55), $P=0.001$] and survival free of heart failure hospitalization 47.5% vs. 67.5% [$P<0.001$, Figure 1c; HR=2.30 (95% CI 1.45–3.65), $P<0.001$]. In multivariable analysis, the presence of SID was the strongest independent predictor for survival and survival free of heart failure

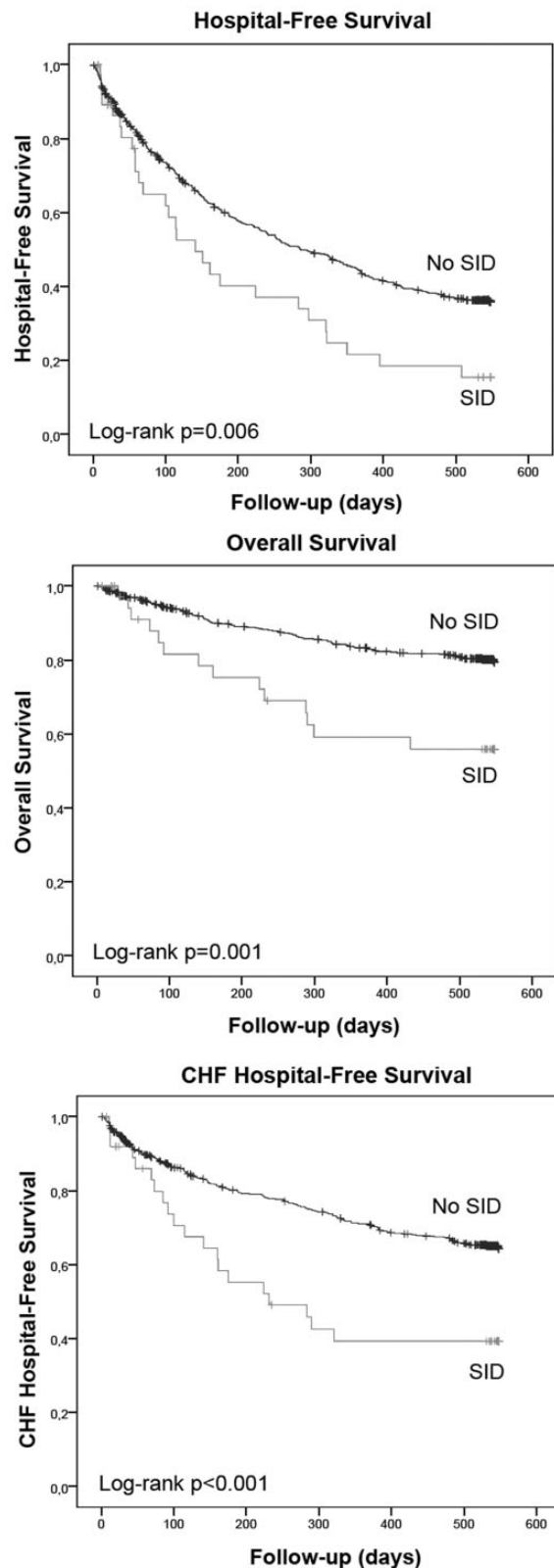


Figure 1. (a) Kaplan Meier analysis for the primary endpoint all-cause hospitalization free survival. (b) Kaplan Meier analysis for the secondary endpoints overall survival and (c) CHF hospitalization free survival.

Table 3 Predictors for adverse outcome and HRs in multivariate analysis for the different endpoints

| | HR | 95% CI | P-value |
|-----------------------------------|-------|-------------|---------|
| Hospital-free survival | | | |
| SID | 1.32 | 0.87–2.0 | 0.2 |
| Preserved LVEF | 1.586 | 1.213–2.073 | 0.001 |
| Primary cause CAD | 1.496 | 1.174–1.907 | 0.001 |
| Charlson score | 1.146 | 1.070–1.227 | <0.001 |
| Prednisone use | 1.453 | 1.102–1.916 | 0.008 |
| Angina pectoris at baseline | 1.453 | 1.129–1.87 | 0.004 |
| Anaemia at baseline | 1.311 | 1.045–1.644 | 0.019 |
| Elevated JVP | 1.177 | 1.070–1.296 | 0.001 |
| Serum-creatinine | 1.003 | 1.000–1.006 | 0.037 |
| QRS width | 1.003 | 1.001–1.006 | 0.022 |
| Overall survival | | | |
| SID | 2.951 | 1.651–5.275 | <0.001 |
| Serum NT-proBNP log 10 | 2.275 | 1.359–3.810 | 0.002 |
| Primary cause CAD | 2.136 | 1.394–3.271 | <0.001 |
| Anaemia at baseline | 2.161 | 1.479–3.159 | <0.001 |
| History of syncope | 2.158 | 1.163–4.003 | 0.015 |
| Cancer | 2.104 | 1.364–3.245 | 0.001 |
| Rales on auscultation | 1.548 | 1.225–1.957 | <0.001 |
| NYHA class at baseline | 1.397 | 1.001–1.951 | 0.05 |
| Charlson score | 1.188 | 1.069–1.319 | 0.001 |
| QRS width | 1.009 | 1.004–1.013 | <0.001 |
| NSAID use | 0.424 | 0.244–0.739 | 0.002 |
| CHF-hospital-free survival | | | |
| SID | 2.708 | 1.675–4.377 | <0.001 |
| Cancer | 2.332 | 1.622–3.353 | <0.001 |
| Osteoporosis | 2.127 | 1.401–3.229 | <0.001 |
| Primary cause CAD | 1.955 | 1.438–2.658 | <0.001 |
| History of syncope | 1.904 | 1.208–3.001 | 0.006 |
| Anaemia at baseline | 1.807 | 1.351–2.415 | <0.001 |
| Rales on auscultation | 1.653 | 1.398–1.955 | <0.001 |
| Diabetes mellitus | 1.641 | 1.213–2.220 | 0.001 |
| Serum creatinine | 1.008 | 1.005–1.012 | <0.001 |
| QRS width | 1.007 | 1.003–1.011 | <0.001 |
| NSAID use | 0.675 | 0.456–0.998 | 0.049 |

JVP, jugular venous pressure.

hospitalization, whereas the presence of SID was no longer an independent predictor for all-cause hospitalization free survival (Table 3). Other strong independent predictors for overall survival or survival free of heart failure hospitalization were CAD as main cause of CHF, and history of cancer or syncope. Regarding all-cause hospitalization free survival, the strongest predictors for poor outcome were preserved LVEF and CAD as main cause of CHF.

Analysis of anti-inflammatory drug use revealed that utilization of corticosteroids was an independent predictor for a worse outcome in regard to all-cause hospitalization free survival (HR 1.45, 95% CI 1.1–1.92, $P=0.008$), whereas NSAID use was an independent predictor for better survival (HR 0.42, 95% CI 0.24–0.74, $P=0.002$) and better survival free of heart failure hospitalization (HR 0.68, 95% CI 0.45–0.99, $P=0.049$).

Table 4 Baseline characteristics of patients with NSAID use

| Characteristic | No NSAID use <i>n</i> = 499 | NSAID use <i>n</i> = 123 | <i>P</i> -value |
|--------------------|--------------------------------|-----------------------------|-----------------|
| Age (years) | 76.9 ± 7.5 | 77.1 ± 7.8 | 0.08 |
| Female (%) | 191 (38.3) | 62 (50.4) | 0.014 |
| NT-proBNP (pg/ml) | 4007 (2020–7194) | 3197 (1741–5876) | 0.016 |
| Creatinine (mg/dl) | 117 ± 39 | 110 ± 34 | 0.028 |
| LVEF (%) | 35 ± 13 | 36 ± 13.4 | 0.214 |

Data are given as counts and percentages, mean ± SD or median (interquartile range) as appropriate.

Baseline characteristics of pts with NSAID use are shown in Table 4. Pts receiving NSAID as co-medication were more often female and had lower NT-proBNP and serum creatinine values. There were no differences in terms of age or LVEF between NSAID-users and non-users.

Discussion

To the best of our knowledge, this subgroup analysis of the TIME-CHF study is the first to show that the presence of a SID is strongly associated with poor outcome in elderly patients with CHF. The negative impact of SID could be demonstrated in all analysed endpoints—not only regarding mortality and all cause hospitalization rates but also the more disease specific endpoint of CHF hospitalization free survival. In multivariable analysis including other well established prognostic markers, the presence of SID remained the strongest independent negative predictor for overall survival and survival free of heart failure hospitalization. Given the increasing prevalence of SID in the elderly population, which is also prone to CHF, these findings are clinically important for both risk stratification and patient management.

It is not uncommon that clinicians have to provide health care for patients with SID and CHF. Most relevant epidemiological data about SID focus on specific subgroups and disease entities, respectively. They are derived from unselected patient populations with possibly important ethnic and geographic variations. Nevertheless, it was estimated that almost 22% of all Americans had some form of arthritis or rheumatic condition in 2003–05 with a projected increase in the prevalence up to 40% by 2030.^{9,10} With respect to vasculitic diseases, there is a broad difference in incidence and prevalence according to the specific disease.¹⁴ The most frequently encountered disease entities in our study cohort were PMR/GCA and RA. The prevalence of PMR/GCA is estimated to be 7.4/1000 and 2.8/1000 persons, respectively, over 50 years of age with a

dramatical increase with increasing age. In patients aged 75–79 years, the prevalence is 19.8/1000 and 6.2/1000, respectively, whereas in patients aged 90 years or older, it rises to 40.7/1000 and 17.2/1000, respectively.⁹ For RA, available data suggests that the overall prevalence among adults older than 34 years is ~8.5/1000 persons with an increase with increasing age and a peak prevalence in patients aged 65–74 years (male ~16/1000, female ~24/1000).¹⁰ In our cohort, the cumulative prevalence of SID was 6%, highlighting the frequency of this co-morbidity in elderly CHF patients.

The fact that the presence of SID was the strongest independent negative predictor for survival free of CHF hospitalization and survival but did not predict independently all-cause hospitalization free survival might suggest a disease modifying role of SID in CHF. An inherent feature of SID is the presence of immune activation with elevation of inflammatory cytokines. Among others, elevation of IL-6 and TNF- α is characteristic in SID and may serve as a marker for disease activity.^{15–18} Immune activation with elevation of IL-6 and TNF- α is also one of the key mechanisms implicated in the propagation of myocardial failure. Levels of IL-6 and TNF- α correlate with both severity of CHF and the development of new-onset CHF, thus implicating a pathophysiological role of these mediators in CHF.^{19,20} Mechanistically, IL-6 and TNF- α were shown to impair myocardial contractile function thereby propagating the development of CHF.^{21,22} IL-6 was also found to correlate with LV systolic and diastolic dysfunction in the general population and in patients with RA.²³ Given a pathophysiological role of these inflammatory cytokines in CHF, it is tempting to speculate that an enhanced systemic inflammation triggered by SID may directly influence the course of co-existing CHF. A direct association remains, however, unproven and would have to be tested in a prospective intervention trial. Moreover, inhibition of TNF- α in CHF patients not selected based on inflammation did not improve outcome.²⁴

The use of concomitant medication may negatively influence prognosis. Often, patients with SID are treated with steroids and NSAIDs. In CHF patients, the association between NSAID intake and worsening symptoms is well established. Particularly in elderly CHF patients, the use of NSAIDs has been associated with an up to 10-fold increased risk of worsening CHF requiring hospitalization.²⁵ In our cohort, however, the NSAID use was associated with a better overall survival and survival without CHF hospitalization. This finding should be interpreted with great caution because it may be biased by the possibility that healthier patients received NSAIDs, whereas in sicker patients NSAIDs were withheld—as suggested by the differences in baseline characteristics of those receiving NSAIDs compared to those not receiving NSAIDs. Moreover, NSAIDs were not randomly assigned. Though provocative, our results nevertheless suggest that a prospective study of NSAID use in CHF patients and significant systemic inflammation might be worthwhile considering.

Likewise corticosteroid use may be associated with a worse cardiovascular outcome. Use of therapeutic doses of glucocorticoids are associated with higher rates of myocardial infarction, stroke, CHF and all-cause mortality as shown in large population based studies.^{26,27} Chronic glucocorticoid intake may lead to fluid retention, hypertension, dyslipidemia and hyperglycaemia and thereby may worsen heart failure symptoms and accelerate atherosclerosis.^{28–30} In patients with SID, however, the cardiovascular effects of chronic corticosteroid therapy remain to be determined. In RA patients, there are conflicting data whether corticosteroids have a more favourable effect on cardiovascular outcome by reducing inflammation or an unfavourable effect due to their above-mentioned cardiovascular and metabolic side effects.^{31–34} In our cohort, use of corticosteroids was negatively associated with the combined endpoint of all-cause hospitalization and mortality. Again, these results should be interpreted with caution, due to the presence of potential confounding factors, the limited number of patients receiving chronic corticosteroids in our cohort and the lack of prospective randomized assignment of corticosteroid use.

Intriguingly, we observed that heart failure with preserved ejection fraction (HFpEF) was a strong negative predictor of the primary endpoint all cause hospitalization free survival but not the other endpoints. This observation in the TIME-CHF was recently discussed by Maeder *et al.*³⁵ One possible reason for this observation was that the definition of HFpEF was tighter than in other prospective trials on HFpEF. Thus, the NT-proBNP cut-off

applied in our study was higher than proposed in the most recent recommendations for the diagnosis of HFpEF and the median NT-proBNP of for, e.g. in the PEP-CHF and I-PRESERVED trials. Therefore, we selected a population of patients in whom confidence of HFpEF diagnosis was high, and the patients were sicker than in other HFpEF trials.³⁵

Our study has several limitations. It is a *post hoc* analysis of a prospective trial with a limited number of patients suffering from SID. The presence of co-morbidities including SID was reported by investigators, based on the personal and documented case history. There was no complete documentation of date of first diagnosis, duration of the SID, disease activity and previous treatment. In addition, there was no information about the extent of inflammation at study entry. A significant part of patients was included directly after a CHF related hospitalization and some of them had suffered from concomitant infection. Therefore, C-reactive protein (CRP) levels at inclusion do not necessarily reflect the extent of inflammatory activation triggered by SID. As mentioned, a causative relation between medication and outcome cannot be proven by this retrospective analysis and is hypothesis generating only.

Conclusion

SIDs, in particular PMR/GCA and RA, are common in an elderly CHF population and associated with a poor outcome, which requires special attention. Whether SID has a direct causal influence on prognosis and whether specific treatment of SID may improve outcome in CHF remains to be determined.

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